referred to as "the Cuthbertson reference"). The Office also has maintained the rejection under 35 U.S.C. § 103(a) of claims 1-15, 21, and 24-27 as allegedly being obvious in view of the Bouck reference, the Cuthbertson reference, U.S. Patent 6,113,913 (herein referred to as "the Brough '913 patent"), and U.S. Patent 6,225,113 (herein referred to as "the Brough '113 patent"). Finally, the Office has maintained the rejection under 35 U.S.C. § 103(a) of claims 1, 2, 18-21, and 24-27 as allegedly being obvious in view of the Bouck reference, the Cuthbertson reference, and U.S. Patent 5,962,311 (herein referred to as "the Wickham reference"). Reconsideration of these rejections is hereby requested.

The Amendments to the Claims

Claims 3, 7, and 10 have been cancelled. Applicants reserve the right to pursue any cancelled subject matter in a continuation, continuation-in-part, divisional, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter. Claim 1 has been amended to incorporate the features of claims 4 and 6. Claims 4, 5, 6, 8, and 9 have been amended in view of the amendment to claim 1. No new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the claims, as well as the text of all of the pending claims, are enclosed herewith.

Discussion of the Election/Restriction

The Office has withdrawn claims 16, 17, 22, and 23 from further consideration as being drawn to a nonelected species, since no generic or linking claim has been allowed. Accordingly, the Office alleges that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 C.F.R. § 1.144). In view of the amendments made to the claims, Applicants contend that the generic or linking claims are allowable, such that cancellation of claims 16, 17, 22, and 23 is not necessary. Applicants, therefore, request that these claims continue to be considered.

Discussion of the Rejections under 35 U.S.C. § 103(a)

The Office has maintained the rejection of claims 1, 2, 21, and 24-27 under 35 U.S.C. § 103(a) as allegedly obvious in view of the Bouck reference and the Cuthbertson reference. In particular, the Office relies upon the Bouck reference for its alleged disclosure of SLED, which purportedly includes any anti-angiogenic derivative of PEDF, and for its alleged teaching that SLED can be provided to a tissue of interest by transferring a nucleic acid sequence encoding SLED to cells associated with the tissue of

interest through the use of any suitable vector, such as an adenoviral vector (pages 3-4 of Paper No. 8). The Office relies on the Cuthbertson reference for its alleged disclosure of a method of generating a genetically-engineered *in situ* ocular cell, comprising contacting an ocular cell with an adenovirus vector (pages 4-5 of Paper No. 8). The Office concludes that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to make an adenovirus vector comprising a nucleic acid encoding PEDF or therapeutic fragment thereof or further comprising a nucleic acid sequence encoding other therapeutic substances such as other antiangiogenic substances" (page 5, Paper No. 8). Applicants respectfully traverse this rejection for the reasons set forth below.

In issuing this rejection, the Office has failed to analyze each of the Bouck and Cuthbertson references *as a whole,* and has used impermissable hindsight in establishing motivation to combine the teachings of the cited references. The Manual of Patent Examining Procedure (M.P.E.P.) at Section 2141.02 states: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984)." As a whole, the Bouck reference is directed to SLED polypeptides and methods of inhibiting angiogenesis through administering SLED polypeptides. The specification of the Bouck reference lists several vectors, besides adenoviral vectors, that are suitable for expressing a SLED polypeptide, including plasmids, adeno-associated viral vectors, herpesvirus vectors, packaged amplicons, pappiloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors, vaccinia virus vectors, and other vectors (col. 6, line 59, through col. 7, line 3). As the Bouck reference merely lists adenoviral vectors as one of many "suitable vectors," this reference does not point specifically to adenoviral vectors.

The Cutherbertson reference, as a whole, is directed to gene therapy to any ocular cell for the treatment of any ocular disease. The ocular gene therapy encompasses *both* anti-sense gene therapy and protein expression gene therapy (col. 4, lines 20-22). In the situation where protein expression is desired, the protein is taught to be a "protein associated with an ocular disease" or a "protein useful in the treatment of an ocular disease" (col. 4, line 62). The term "ocular disease" is defined as "a disorder or pathological condition of the eye which is not normal to the animal in a healthy state" (col. 4, lines 63-65). The Cuthbertson reference lists numerous ocular diseases as falling within the definition, which range from genetic diseases to disorders caused by infection

to non-genetic progressive diseases and which involve any and all layers of the eye. (col. 4, line 66, through col. 5, line 30). As the Cuthbertson reference lists a multitude of ocular diseases, the number of proteins associated with or useful for the treatment of these ocular diseases is, accordingly, multitudinous. The Cuthbertson fails to point to a particular disease, let alone a particular protein. Furthermore, the Cuthbertson reference lists other means of expressing proteins in the eye, including retroviral infection, transformation with plasmids, transformation with liposomes containing exogeneous nucleic acid, biolistic nucleic acid delivery, adenoassocited viral infection, and Epstein-Barr viral infection (col. 6, lines 16-25).

A consideration of the cited references *as a whole* reveals that the presently claimed invention is unobvious over the combination of the cited references inasmuch as there is no teaching or reasonable suggestion *in the cited references* to combine their disclosures in the *precise manner* required to result in the present invention. The Federal Circuit has held that combining prior art references without evidence of a suggestion, teaching, or motivation to combine the references, *even where* all elements of the claimed invention are taught in the prior art, "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability –the essence of [impermissible] hindsight." *In re Dembiczak,* 175 F3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). The Federal Circuit emphasized that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing [i.e., actual evidence] of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617. Moreover, the Federal Circuit held some time ago that "one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988).

Although the Office alleges that one of ordinary skill in the art would have been motivated to combine the teachings of the Bouck and Cuthbertson references "for the expected benefit of making an adenoviral vector useful for treating a variety of eye diseases" (page 5 of Paper No. 8), neither the Bouck reference nor the Cuthbertson reference teaches the desirability of combining the teachings of the two references, let alone in the precise manner necessary to provide the present invention. As stated in the M.P.E.P. at Section 2143.01, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 916 F.2d 680, 16 USPQ2d

1430 (Fed. Cir. 1990). Therefore, the present inventive adenoviral vector comprising a nucleic acid encoding PEDF or a therapeutic fragment thereof is unobvious in view of the Bouck and Cuthbertson references.

However, in order to advance prosecution and not in acquiescence of the rejection, Applicants have amended claim 1 to recite the limitations of claims 4 and 6, thereby specifying that the present inventive replication defective adenoviral vector lacks all or part of the E1 region and all or part of the E4 region. As the Office admits that "Bouck et al. and Cuthbertson do not specifically teach particular types of replication defective adenoviral vectors" (see page 7 of Paper No.8), the combination of the Bouck reference and the Cuthbertson reference, therefore, does not render obvious the subject matter of amended claim 1. Furthermore, since all of the other claims are dependent on claim 1, either directly or indirectly, Applicants submit that the combination of the Bouck and Cuthbertson references also does not render obvious the subject matter of any of the other pending claims (e.g., claims 21 and 24-27). Applicants, therefore, request that the rejection of claims 1, 21, 24-27 under Section 103(a) be withdrawn.

The Office also has maintained the rejection of claims 1, 2, 18-21, and 24-27 under 35 U.S.C. § 103(a) as allegedly obvious in view of the Bouck reference, the Cuthbertson reference, and the Wickham reference. In particular, the Office states that it would have been obvious at the time the invention was made to modify the adenoviral vector made from the combined teachings of the Bouck reference and the Cuthbertson reference to comprise a chimeric adenovirus fiber in that the Wickham reference purportedly teaches that it is within the ordinary skill in the art to make adenoviral vectors further comprising a chimeric coat protein having an inserted non-native sequence which directs the entry of the adenovirus to particular cells (pages 15-16 of Paper No. 8). Applicants respectfully traverse this rejection. The Wickham reference does not satisfy the aforementioned deficiencies of the Bouck and Cuthbertson references. In particular, the Wickham reference does not provide the motivation and direction to combine the disclosures of Bouck and Cuthbertson references, let alone in the precise manner necessary to provide the present invention. Moreover, the Wickham reference, like the Bouck and Cuthbertson references, does not teach or suggest an adenoviral vector deficient in all or part of the E1 region and all or part of the E4 region. The combination of the three references, therefore, does not render obvious an adenoviral vector comprising a nucleic acid encoding PEDF or a therapeutic fragment thereof and lacking all or part of the E1 region and all or part of the E4 region. In view of the

foregoing, Applicants request that the rejection of claims 1, 2, 18-21, and 24-27 under U.S.C. § 103(a) be withdrawn.

The Office has maintained the rejection of claims 1-15, 21, and 24-27 under 35 U.S.C. § 103(a) as allegedly obvious in view of the Bouck reference, the Cuthbertson reference, the Brough '913 patent, and the Brough '113 patent. In particular, the Office relies upon the Brough '913 patent for the alleged disclosure of recombinant adenoviral vectors deficient in E1A or E1B in combination with a deficiency in the E2 region and/or the E3 region and/or the E4 region. The Office relies on the Brough '113 patent for the alleged disclosure of recombinant adenoviral vectors deficient in the E4 region and comprising a gene encoding a trans- or cis-acting factor. The Office states that, in view of these disclosures, "[i]t would be obvious to one of ordinary skill in the art to make an adenoviral vector made from the combined teachings of Bouck et al and Cuthbertson because both Brough et al references teach that it is within the ordinary skill in the art to make replication defective adenoviral vectors and defective adenoviral vectors further comprising a gene encoding a trans-acting factor like HSV ICP0, and cis-acting factors such as MAR and LAR" (pages 11-12 of Paper No. 8). Applicants respectfully traverse this rejection for the reasons set forth below.

The filing date of the instant application is after November 29, 1999. 35 U.S.C. § 103(c) mandates that, effective November 29, 1999, subject matter developed by another which qualifies as prior art only under one or more of subsections (e), (f), and (g) of 35 U.S.C. § 102 is not to be considered when determining whether an invention sought to be patented is obvious under 35 U.S.C. § 103, provided that the subject matter and the claimed invention were commonly owned at the time the invention was made. The Brough '913 patent and the Brough '113 patent qualify as prior art to the instant application only under 35 U.S.C. § 102(e), and both are commonly owned by the assignee of the instant application. As a result, it is improper to cite the Brough '913 patent and/or the Brough '113 patent as a basis for rejection under Section 103.

In any event, Applicants contend that it is not obvious to one of ordinary skill in the art to make or use the adenoviral vector of the pending claims in view of the Bouck reference, the Cuthbertson reference, the Brough '913 patent, and the Brough '113 patent. The Brough '913 and '113 patents do not satisfy the aforementioned deficiencies of the Bouck and Cuthbertson references. In particular, the Brough '913 and '113 patents do not provide the motivation and direction to combine the disclosures of Bouck and Cuthbertson references, let alone in the precise manner necessary to provide the present invention. Indeed, since the prior art available prior to filing of the instant application

teaches away from the presently claimed invention by disclosing that the deletion of the E4 region can be disadvantageous with respect to persistent gene expression. See, for example, Brough et al., *Journal of Virology* 71: 9206-9213 (1997), enclosed herewith, which discloses that an adenoviral vector having a deletion of the E1 region and E4 region of the adenoviral genome demonstrates lower sustained expression levels, as compared to an analogous adenoviral vector retaining the E4 region. Because the Brough et al. reference teaches the importance of the E4 region for sustained expression levels, this reference teaches away from the present inventive adenoviral vectors lacking all or part of the E4 region. Therefore, one of ordinary skill in the art would not be motivated to remove all or part of the E4 region to arrive at the presently claimed invention.

In view of the foregoing, Applicants submit that the present inventive replication defective adenoviral vector, which comprises a nucleic acid encoding PEDF or a therapeutic fragment thereof and lacks all or part of the E1 region and all or part of the E4 region, is not obvious. Therefore, Applicants request that the rejection of claims 1-15, 21, and 24-27 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,

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Date: December 19, 2002

In re Appln. of Kovesdi et al.
Application No. 09/599,997

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: December 19, 2002 Kim Moreau